replacing hylauronic acid "derivatives" with "esters." Claims 1 and 7 have been amended to recite hyaluronic acid "esters." Basis for these amendments appears in the specification; for example, on page 2, line 27; page 3, line 21 through page 4, line 2; and page 7, lines 5-10. Claims 1 and 7 have also been amended to recite an "injectable composition" as opposed to "a composition for injectable delivery." Basis for these amendments appears throughout the specification; for example, on page 1, lines 9-11 and page 3, lines 20-25. Claim 3 has been amended to indicate that suitable pore-forming agents allow "in situ pore formation following injection of the composition." Basis for this amendment appears in the specification; for example, on page 4, lines 3-9. New claim 11 is presented again because it is Applicants' understanding that claim 11 does not raise new issues that would require further consideration and/or search. Claim 11 depends from claim 2 and further comprises a pore-forming agent. Therefore, consideration and search of this claim overlaps with that of claim 2 and 3. Basis for claim 11 is found in the specification; for example, on page 3, line 19 through page 4, line 10. During a telephone conference with the undersigned attorney, the Examiner indicated that he would consider claim 11 in this response and that presentation of claim 11 herein would not pose a concern with respect to his consideration of the response.

In addition to the Version With Markings to Show Changes, for convenience, Applicants have also provided herewith an Appendix setting forth the claims pending as

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amended.

Rejection Under 35 USC §112

The Examiner maintains the rejection of claims 1-7 as being indefinite contending that the term "derivative," though commonly used in the art, does not have a set or clear meaning. Claims 1 and 7 have been amended to replace the term "derivative" with "ester," thereby overcoming the rejection.

The Examiner contends that the term "pore-forming agent" is very broad and that "pore-forming agents range from chemical to physical." Applicants have amended claim 3 to further indicate that suitable pore forming agents "allow in situ pore formation following injection of said composition." Basis for this amendment is found in the specification; for example, on page 4, lines 3-8. Suitable liquid pore formers are disclosed such as polyethylene glycol and solid pore formers such as sodium bicarbonate, sodium chloride citric acid, and sucrose. Applicants submit that such pore-forming agents are known to those skilled in the art and the selection of suitable agents is within the knowledge of one skilled in the art. U.S. Patent No. 5,939,323, cited by the Examiner, for instance, discloses such pore-forming agents.

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Rejections Under 35 USC §102

The Examiner maintains the rejection of claims 1, 2, 4, and 7 as allegedly anticipated by Vanis et al. for disclosing a mixture comprising calcium phosphate, hyaluronic acid, and BMP. Claims 1 and 7 as amended recite hyaluronic ester, which is neither disclosed nor suggested by Vanis et al. Furthermore, the material disclosed by Vanis et al. is not injectable, contrary to the Examiner's contention. Rather, Vanis et al. refers to a material that is "suitable for bone implants" and "is formed into desired implant shape" (see Abstract). The claimed invention is distinguishable from Vanis et al. by its suitability for closed fracture repair without an open reduction procedure as is necessary with implantation. Furthermore, it is noted the Vanis et al. material requires the calcium phosphate and/or calcium fluorophosphate particles to be mixed with atelocollagen I (see Abstract), whereas claim 2 requires merely osteogenic protein, hyaluronic ester and tricalcium phosphate. Therefore, the claimed invention is not anticipated by Vanis et al.

Rejections Under 35 USC 103

The Examiner maintains the rejection of claims 1-7 as unpatentable over Wozney et al. (U.S. Patent No. 6,187,742) for disclosing the combination of elements of

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Applicants' claimed composition. The Examiner contends that the fact that Wozney et al disclose the components in the alternative is motivation to pick and choose from among those to obtain the claimed invention.

Claims 1 and 7 have been amended to recite hyaluronic acid "esters", which are neither taught nor suggested by Wozney et al. Furthermore, it is noted that Wozney et al., is directed to a method for regeneration of a functional attachment between ligament and bone comprising administering BMP. Numerous materials, which may be useful as carriers, are described in Woznet et al. such as collagenous materials and porous particulate polymers. In addition, sequestering agents are disclosed such as cellulosic material, hyaluronic acids, and sodium alginate among a list of many others - with the preferred agent being carboxymethyl cellulose. Hyaluronic acid is also included among the list of suitable carriers in addition to surgical mesh sutures and demineralized bone. Several modes of administration are disclosed such as application with a brush or injection.

The presently claimed injectable composition comprising BMP and hyaluronic acid esters is neither taught nor suggested by Wozney et al. As the Examiner states, Applicants' claimed invention is not exemplified and Applicants submit that it not obvious based on Wozney et al., to find and select the individual elements of Applicants invention within the lists of many suitable carriers, sequestering agents, and modes of

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administration set forth in Wozney et al., which do not even include hyaluronic acid esters, with the reasonable expectation of success in promoting the formation of cartilage and/or bone and or the repair of tissue damage or fracture repair.

The Examiner maintains the rejection of claims 1, 2, and 4-7 as unpatentable over Rhee et al. (U.S. Patent No. 5,752,974) for disclosing the combination of BMP-2 or BMP-7, PEG, a cross-linked hyaluronic acid or hyaluronic acid, and tricalcium phosphate designed for injection. Claims 1 and 7 as amended recite "hyaluronic acid esters" which are not disclosed by Rhee et al. Furthermore, the disclosure of tricalcium phosphate in Rhee et al. is with respect to an injectable composition comprising collagen and a biocompatible ceramic wherein the preferred ceramics include calcium phosphate and tricalcium phosphate(see column 6, lines 49-57). Collagen is not an element of Applicants' claimed composition.

The Examiner maintains the rejection of claims 1-5 and 7 as unpatentable over Valentini et al. (U.S. Patent No. 5,939,323). The presently-claimed invention is directed to injectable compositions, whereas Valentini et al. disclose implantable compositions. The "solution" referred to in Valentini et al., which the Examiner contends is injectable, actually refers to a blending of solutions prior to formation of the scaffold which is then implanted (see, for example, column 6, line 62 through column 7, line 21). *Implantation* of the scaffold is described throughout the specification for example in column 7, line

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43, column 9 line 38, and column 11, line 36. Applicants submit therefore that the claimed invention is patentable over Valentini et al.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully request reconsideration of the application. Should the Examiner consider that the claims are not in condition for allowance, Applicants request that the Examiner telephone the undersigned at (617) 452-1661 to further discuss the application. Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Date: September 10, 2002

By: Leslie McDonell (Reg. No. 34,872)
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Version With Markings to Show Changes Made

Claims 1, 3, 7 and 11 have been amended as follows:

1. (Twice amended) An injectable composition for ~~injectable~~ delivery of osteogenic proteins comprising a pharmaceutically acceptable admixture comprising

(a) an osteogenic protein; and

(b) an injectable hyaluronic acid ester ~~derivative~~.

3. (Twice amended)The composition of claim 1 further comprising a pore-forming agent wherein said pore-forming agent promotes in situ pore formation following injection of said composition.

7. (Amended) An injectable composition for ~~injectable~~ delivery of osteogenic proteins comprising a pharmaceutically acceptable admixture comprising

(a) BMP-2;

(b) an injectable hyaluronic acid ester ~~deriviative; and~~

~~(c) tricalcium phosphate~~.

11. (New) The composition of claim 2 further comprising a pore-forming agent wherein said pore-forming agent promotes in situ pore formation following injection of said composition.

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APPENDIX OF CLAIMS PENDING AS AMENDED

1. An injectable composition for delivery of osteogenic proteins comprising a pharmaceutically acceptable admixture comprising
   (a) an osteogenic protein; and
   (b) an injectable hyaluronic acid ester.
2. The composition of claim 1 further comprising tricalcium phosphate.
3. The composition of claim 1 further comprising a pore-forming agent wherein said pore-forming agent promotes in situ pore formation following injection of said composition.
4. The composition of claim 1 wherein the osteogenic protein is selected from the group consisting of members of the BMP family.
5. The composition of claim 4 wherein the osteogenic protein is BMP-2.
6. The composition of claim 4 wherein the osteogenic protein is OP-1.
7. An injectable composition for delivery of osteogenic proteins comprising a pharmaceutically acceptable admixture comprising
   (a) BMP-2;
   (b) an injectable hyaluronic acid ester.
11. The composition of claim 2 further comprising a pore -forming agent wherein said pore-forming agent promotes in situ pore formation following injection of said composition.

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